REMARKS

I. Status

With entry of this amendment, Claims 4 and 17-26 are pending. Claims 1-3 and 5-16 have been cancelled without disclaimer or prejudice to prosecution of the claimed subject matter in this or a future application.

Claims 4, 18 and 25 are amended to correct typographical errors. Claim 25 is amended to depend from Claim 24. Claim 18 is amended to recite, inter alia, that administration of a $GABA_B$ receptor antagonist is the treatment of the patient. Support for the amendment to Claim 18 is provided in the specification, for example, at page 4, last paragraph and page 6, second paragraph. No new matter is added by these amendments.

II. Rejection under 35 U.S.C. § 112, second paragraph

Claims 4 and 17-25 stand rejected as allegedly indefinite. The Office alleges the claims require a therapeutically effective amount of a $GABA_B$ receptor antagonist, but fails to stipulate what the amount is effective for. Applicants respectfully traverse. As an initial matter, only independent Claim 18, and the claims depending therefrom, recite a "therapeutically effective amount." In claims 4, 17, 19, 21, 22, 24 and 25 an amount of a $GABA_B$ receptor antagonist "sufficient to increase neurotrophin levels in the CNS of a patient with Parkinson's disease" is administered. Thus, each claim must be considered individually to determine whether it is or is not indefinite.

Claims 4 and 17-25 are not indefinite

The Office contends claims 4 and 17-25 are indefinite because allegedly the claims do not stipulate what the amount of the $GABA_B$ receptor antagonist is effective for. In particular, the Office contends the claims are indefinite because there is no requirement that the amount is effective for treating Parkinson's disease. Applicants respectfully traverse the rejection.

A claim is definite if, when read in light of the specification, it reasonably apprises those skilled in the art of the scope of the invention. *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385, 1406 (Fed. Cir. 2003); MPEP § 2173.02.

Claims 4 and 17 set forth clearly the amount of $GABA_B$ receptor antagonist to be administered, i.e., an amount sufficient to increase neurotrophin levels in a patient with Parkinson's disease (also see the specification at page 1, second paragraph and page 4,

last paragraph). This is not indefinite. A rejection similar to the one made by the Office in this case was addressed by the Board of Patent Appeals and Interferences in *In re Skuballa*, 12 USPQ2d 1570, 1571 (Bd. Pat. App. Int. 1989). In *Skuballa*, claim 20 recited "[a] method of inhibiting gastric acid secretion or for cytoprotection in a patient comprising administering an effective amount of a compound of claim 1 to the patient." Id. at 1572. The examiner alleged the claims were "*indefinite in the recitation of 'an effective amount' since they fail to state the function to be achieved by the amount of the claimed compound.*" Id. at 1571. The Board reversed the rejection, stating "*[w]e are unable to subscribe to the examiner's contention [that the claims are indefinite], particularly as to the method of use claims, namely claims 20 and 21 which set forth the function or functions to be achieved by administering the claimed [] compounds to the patient.*" Id. at 1571. Similarly, in the instant application Claims 4 and 17 *set forth the function* (increasing neurotrophin levels) to be achieved by administering the $GABA_B$ receptor antagonist. Applicants respectfully submit claims 4 and 17 are not indefinite.

The Office also states "*Additionally claims 4 and 17 . . . require a method for increasing neurotrophin levels in a patient with Parkinson's disease, yet the claim language does not specifically require that the methods provide any benefit regarding the symptoms or causes of the Parkinson disease, thus it is unclear if the claims encompass treatment of Parkinson disease.*" Applicants disagree. It is completely clear that if a treatment of Parkinson's disease comprises administering an amount of $GABA_B$ receptor antagonist sufficient to increase neurotrophin levels to a patient, that treatment is encompassed by the claims. Alternatively, if the treatment of Parkinson's disease does not involve administering a $GABA_B$ receptor antagonist, that treatment is not encompassed by the claims.

Applicants acknowledge that the Office also asserts the specification is not enabling for treating a patient with Parkinson's disease (discussed below). Applicants also note that increasing neurotrophin levels in a Parkinson's patient is intended to provide a therapeutic benefit to the patient (e.g., see claim 18). However, concerns about enablement (whether or not warranted) do not render a claim indefinite. Applicants request this rejection be withdrawn.

Claim 18 was also rejected as indefinite because, although the claim recites that a therapeutically effective amount of a $GABA_B$ receptor antagonist is administered, it allegedly does not stipulate what the amount is effective for. Applicants submit that the decision in *In re Skuballa*, discussed above, applies. Applicants respectfully submit the skilled artisan would understand the phrase "therapeutically effective amount" requires an

amount sufficient to effect treatment of Parkinson's disease in the patent (e.g., alleviate a symptom or reduce progression of the disease). Applicants submit no more is required, and that Claim 18, and the claims depending therefrom, are definite.

Without acquiescing to this rejection, but to expedite prosecution of this case, Applicants amend Claim 18 to recite that administering to a patient in need of such treatment a therapeutically effective amount of a GABAB receptor antagonist is treatment of the patient. Applicants submit this rejection is moot in view of the amendment.

III. Claim Objections

Claim 24

Claim 24 is objected to for allegedly failing to further limit Claim 4. Applicants traverse this objection. Independent Claim 4, as amended, recites a method for increasing neurotrophin levels in the central nervous system (CNS) of a patient with Parkinson's disease, amyotrophic lateral sclerosis or stress-induced neurodegeneration. Dependent Claim 24 recites the patient has Parkinson's disease or amyotrophic lateral sclerosis. Thus, Claim 24 properly further limits Claim 4.

Claim 25

Claim 25 is objected to for allegedly failing to further limit Claim 18, from which it indirectly depends. Applicants submit this objection is moot in view of the amendment to Claim 25, which now depends from Claim 24.

Applicants therefore request the Office to reconsider and withdraw these rejections and objections of the claims.

IV. Rejection under 35 U.S.C. § 112, first paragraph:

Claims 4 and 17-25 stand rejected as allegedly lacking enablement for methods of treating Parkinson's disease and for allegedly lacking enablement for any meaningful use for methods of increasing neurotrophin levels in Parkinson's patients, "wherein this increase does not provide a treatment for Parkinson's disease." Applicants respectfully traverse both of these theories of nonenablement.

As is discussed in detail below, Applicants believe the specification is enabling of Claims 18, 20, and 23, directed to a method of treating Parkinson's Disease.

Applicants also believe, and the Office has not disputed, that the specification

teaches a method of increasing CNS neurotrophin levels (see, for example, the specification at pages 3 and 4, disclosing experiments in an animal model showing increased neurotrophin expression after administration of a $GABA_B$ receptor antagonist). The Office has not disputed that the specification teaches now to increase neurotrophin levels by administering a $GABA_B$ receptor antagonist. The Office has instead opined "*the specification [does not] provide any meaningful use for methods of increasing neurotrophin levels in Parkinson's patients wherein this increase does not provide a treatment of Parkinson's disease.*" If it is the position of the Office that (a) increasing neurotrophin levels has no use other than for treating Parkinson's patients and (b) it is not credible that increasing neurotrophin levels would provide benefit in Parkinson's disease, the Office can address in a rejection under Sec. 101, alleging that claim 18 lacks utility.[1] However, this reasoning is not a basis for the instant rejections under Sec. 112, first and second paragraphs. Applicants believe, however, that in addressing the outstanding enablement rejections (below) the concerns of the Office will be addressed.

Turning now to the rejection under Sec. 112, first paragraph:

Enablement is determined by the scope of the claims

Enablement is based on the claimed invention. MPEP 2164 ("The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular claim or application."). Thus, in any rejection, the Office must establish a *prima facie* case of non-enablement based on the instant claims, and not by reading in additional limitations from the specification. As discussed above, independent Claims 4 and 17 require administration of an amount of a $GABA_B$ receptor antagonist sufficient to increase neurotrophin levels. Claim 18 recites administering a therapeutically effective amount of a $GABA_B$ receptor antagonist. Thus, the enablement of each claim must be considered individually.

Only objective enablement is required

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." "Nothing more than objective enablement is required." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). It is therefore irrelevant whether the teaching of the claimed invention is provided through broad terminology or illustrative examples. Id.

[1] If the Office indeed asserts the claims lack utility, Applicants respectfully request that the undersigned be contacted to arrange an interview.

Applicants submit the pending claims are fully enabled. The specification describes the relationship between administration of $GABA_B$ receptor antagonists and an increase in neurotrophin mRNA and protein levels (e.g., NGF and BDNF) in a rat model. See pages 3 and 4 of the Specification. The Office does not challenge the validity of this discovery. The specification also explains the known relationship between neurotrophins and neuroprotection in Parkinson's Disease and other neurodegeneration models. For example, the specification explains that neurotrophins are known to be involved in neuronal survival, and the growth and differentiation of synaptic efficacy and plasticity. See page 1 of the Specification. The specification further explains that neurotrophins can reduce or prevent age-related axotomy, and neurotoxin-induced neuronal loss or reduced function in a variety of brains regions. Id. These relationships are supported by citations in the instant specification and additional supporting citations were set forth in Applicants' response to the prior office action. Applicants will not repeat that response here, but instead refer the Office to two exemplary references confirming the known relationship between neurotrophins and neuroprotection.

Siegel et al., 2000, "Neurotrophic factors in Alzheimer's and Parkinson's disease brain," Brain Res. Rev. 33:199-227, summarizes earlier studies in the MPTP- and 6-OHDA-lesioned animal models of Parkinson's disease. Siegal reports that "*[i]n MPTP- and 6-OHDA-lesioned animal models of Parkinson's disease, BDNF and GDNF have been shown to promote the survival of mesencephalic dopaminergic neurons.*" Id. at 212. Thus, Siegel et al. confirms that increasing neurotrophin levels provides a benefit to Parkinson's patients. BDNF is one of the neurotrophins that is increased by administration of $GABA_B$ receptor antagonists. See Specification at page 4.

Bradford et al., 1999, "Neurotrophins in the Pathogenesis and Potential Treatment of Parkinson's disease," Parkinson's Disease Advanced in Neurology 80:19-25, also established in animal models of Parkinson's Disease that neurotrophins have a beneficial effect. Bradford reports that neurotrophic factors (neurotrophins) provide protection of dopaminergic neurons in an MPTP-model of Parkinson's Disease. Bradford concludes "*[t]he potent protective actions of exogenous neurotrophins towards dopaminergic neurons, together with their trophic support of these neurons, indicate that neurotrophins could be useful therapeutic agents in the treatment* ***if they could be delivered to the target sites in the brain.***" Id. at page. 22 (emphasis added). Applicants' present invention overcomes the problem noted by Bradford by the administration of $GABA_B$ receptor antagonists, which increase levels of neurotrophins in the brain.

Therefore, Applicants submit Claims 4 and 17, and the claims depending

therefrom, are objectively enabled because Applicants demonstrate that administration of $GABA_B$ receptor antagonists increases neurotrophin mRNA and protein levels in an animal model.

Applicants further submit they have objectively enabled Claim 18, and the claims depending therefrom. As discussed above, the specification provides data demonstrating that administration of $GABA_B$ receptor antagonists increases neurotrophin mRNA and protein levels in a rat model. This increase in neurotrophin levels, coupled with the known, beneficial relationship between neurotrophins and neuroprotection in Parkinson's Disease, shows that administration of a therapeutically effective amount of $GABA_B$ receptor antagonists provides a therapeutic benefit in Parkinson's patients.

Applicants are not required to perform clinical trials

The Office's assertions that Applicants' specification is "speculative" and "no data of any kind is provided" (Office Action page 4) is misplaced. As discussed above, the specification provides data demonstrating that administration of $GABA_B$ receptor antagonists increases neurotrophin levels in a rat model. This increase in neurotrophin levels, coupled with the known, beneficial relationship between neurotrophins and neuroprotection in Parkinson's Disease establishes that administration of a sufficient or therapeutically effective amount of $GABA_B$ receptor antagonists to Parkinson's patients provides a benefit. It is well established that Applicants are not required to perform clinical trials to demonstrate utility or enablement. For example, in *In re Brana* the Federal Circuit reversed a rejection in which the Office alleged claims were not enabled because the application did not prove a claimed pharmaceutical compound was useful. *In re Brana*, 34 USPQ2d 1436, 1440 (Fed. Cir. 1995). However, the Court rejected the Office's argument that animal tests were not sufficient to enable the claimed invention. The Court noted "[t]he Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." Id. at 1442.

For the same reasons, Applicants are not required to provide clinical data for the treatment of Parkinson's Disease. Instead, as discussed above, Applicants have used a rat model to demonstrate administration of $GABA_B$ receptor antagonists increases neurotrophin levels. This increase, coupled with the known beneficial relationship between neurotrophins and neuroprotection in Parkinson's animal models, is sufficient to objectively enable the claims.

The Zeevalk reference has not "done the experiment"

The Office alleges that Zeevalk proves the claims are not enabled because Saclofen allegedly was without effect on a malonate-induced toxicity model of striatal dopamine neurons in a rat model of Parkinson's disease. The Office argues that because Zeevalk has allegedly "done the experiment," the claims are not enabled.

Applicants submit the Office misinterprets Zeevalk. Zeevalk reports an observation concerning the effect of saclofen on malonate-induced release of the neurotransmitters GABA and dopamine. Zeevalk describes an experiment involving infusion of saclofen and malonate to the striatum by cannulization so the tip of the cannula is located directly above the striatum. Thus, Zeevalk describes local administration of saclofen to the striatum, and monitors levels of the neurotransmitters GABA and dopamine.

Parkinson's disease is characterized by the selective degeneration of dopaminergic neurons in the substantia nigra and a resulting depletion of striatal dopamine. See, e.g., Siegel et al. (supra), at page 211. As discussed above, neurotrophins can provide neuroprotection to dopaminergic neurons in the substantia nigra. See Siegel et al. (supra); Bradford et al. (supra). Zeevalk does not assay for the beneficial (neuroprotective) effect of neurotrophins in substantia nigra by administration of saclofen. Thus, Zeevalk conducts a very limited experiment the results of which do not indicate that administration of a $GABA_B$ receptor antagonist is useful for treating Parkinson's disease. Accordingly, the Office has not made a prima facie case for nonenablement.

Furthermore, administration of a compound directly to the striatum is quite different from administering a compound to the substantia nigra (or systemically). For example, an earlier paper, Zeevalk et al., 2000, "NMDA Receptors Modulate Dopamine Loss due to Energy Impairment in the Substantia Nigra but not Striatum," Experimental Neurology 161:638-646, reported a difference in the effect of an NMDA receptor antagonist on the substantia nigra and the striatum. When an NMDA receptor antagonist was administered to the substantia nigra in a malonate toxicity model, protection against dopamine loss due to malonate infusion was observed. See page 641, left column. In contrast, administration of the NMDA receptor antagonist to the striatum did not provide a protective effect. Id. Thus, using an NMDA receptor antagonist Zeevalk et al., 2000 demonstrated that a compound that has no effect on the striatum when administered locally may have an effect substantia nigra, establishing that the site of administration

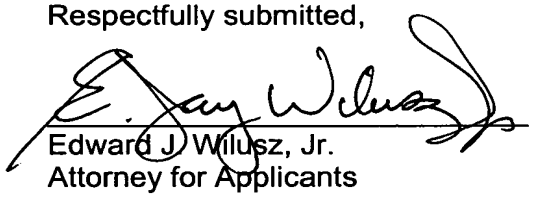
must be considered. Because the Zeevalk 2002 reference cited by the Office does administers the $GABA_B$ receptor antagonist only to the striatum, and measures the effect only in the striatum, that reference does not support the Office's assertion of non-enablement. Accordingly, the Office has not established a *prima facie* case for nonenablement.

Applicants therefore request the Office to reconsider and withdraw this rejection of the claims.

V. Request for Interview

The Applicants therefore believe that the application is now in condition for allowance and respectfully request early notice to that effect. Should the Examiner believe any issues remain, Applicants respectfully request the Examiner to contact the Applicants' undersigned counsel at the telephone number listed below to arrange for an interview to expedite prosecution.

Respectfully submitted,



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